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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/005,220	12/04/2001	Keith D. Allen	R-741	6858

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DELTAGEN, INC.
740 Bay Road
Redwood City, CA 94603

EXAMINER

PARAS JR, PETER

ART UNIT	PAPER NUMBER
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1632

DATE MAILED: 03/08/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/005,220

Applicant(s)

ALLEN, KEITH D.

Examiner

Peter Paras, Jr.

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
 - If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
 - If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
 - Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 14 and 25-41 is/are pending in the application.
- 4a) Of the above claim(s) 39 is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 14 and 25-41 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 04 December 2001 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. ____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. ____. |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date <u>1003</u> . | 6) <input type="checkbox"/> Other: ____. |

DETAILED ACTION

Applicant's preliminary amendment received on 12/3/02 has been entered. Claims 1-13 and 15-24 have been cancelled. Claim 14 has been amended. New claims 25-41 have been added. Claims 14 and 25-41 are pending.

Election/Restrictions

Restriction to one of the following inventions is required under 35 U.S.C. 121:

- I. Claims 14, 25-38 and 40-41, drawn to a transgenic mouse comprising a disruption in an endogenous RPTPB gene, a method of producing the same mouse, and cells comprising a disruption in an endogenous RPTPB, classified in classes 800, 800, and 435, subclasses 18, 21 and 325.
- II. Claim 39, drawn to a targeting construct for an RPTPB gene, classified in class 435, subclass 320.1.

Inventions I and II are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions are materially different products having different functions. For example the transgenic mouse of Group I can be used as a disease model while the targeting construct of Group II can be used for disrupting an RPTPB gene in a cell *in vitro*. Because these inventions are distinct for the reasons given above and have acquired a separate status in the art because of their recognized

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divergent subject matter, different classification, and separate search requirement, restriction for examination purposes as indicated is proper.

During a telephone conversation with Robert Driscoll on 2/10/04 a provisional election was made without traverse to prosecute the invention of Group I, claims 14, 25-38, and 40-41. Affirmation of this election must be made by applicant in replying to this Office action. Claim 39 is withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Sequence Compliance

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached **Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures**.

Applicants are required to comply with all of the requirements of 37 C.F.R. §§ 1.821 through 1.825. Any response to this Office Action, which fails to meet all of these requirements, will be considered non-responsive. The nature of the noncompliance with the requirements of 37 C.F.R. §§ 1.821 through 1.825 did not preclude the examination of the application on the merits, the results of which are communicated below.

Drawings

The drawings filed on 12/4/01 are accepted.

Claim Objections

Claim 40 is objected to as it depends from a non-elected claim.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claim 40 is rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claim is directed to a murine embryonic stem cell comprising a disruption in a RPTPB gene the scope of which is interpreted to read on a murine embryonic stem cell *in vivo*, which embraces a mouse or rat comprising a naturally occurring disruption in an RPTPB gene. Amending the claim to read on an isolated murine stem cell may be sufficient to overcome the instant rejection.

Claims 14, 25-38, and 40-41 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a substantial and specific asserted utility or a well-established utility.

The claims are directed to a transgenic mouse comprising a disruption in an endogenous RPTPB gene wherein the mouse exhibits embryonic lethality, wherein lethality occurs at E9.5-10.5 and the embryo exhibits reduced vascular development

The instant specification has contemplated that the nucleotide sequence set forth in SEQ ID NO: 1 encodes a RPTPB gene. The instant specification has further contemplated that disruption of the nucleotide sequence set forth in SEQ ID NO: 1 in a mouse will produce a phenotype related to RPTPB. The instant specification has purported that such mice may be used to identify agents that modulate or ameliorate a phenotype associated with a disruption in SEQ ID NO: 1.

The instant specification has disclosed a heterozygous transgenic mouse whose genome comprises a disruption in SEQ ID NO: 1 [that does not exhibit a phenotype], wherein a mouse embryo whose genome comprises a homozygous disruption in SEQ ID NO: 1 exhibits embryonic lethality, wherein lethality occurs at E9.5-10.5 and the embryo exhibits reduced vascular development. The claims embrace such a mouse and a method of making the mouse. The instant specification has discussed that phenotype, such as embryonic lethality exhibited by such a transgenic mouse could correlate to a disease or disorder. However, the evidence of record does not provide a correlation between the observed embryonic lethality and any disease or disorder. Moreover, while the specification has purported that the nucleotide sequence set forth in SEQ ID NO: 1 encodes a RPTPB, the evidence of record has failed to provide a correlation between any RBTPB related disease/disorder and embryonic lethality. The specification has provided general assertions that the claimed transgenic mice may be used to identify agents that affect a phenotype related to the mice.

As such, the asserted utility, for the transgenic mouse embraced by the claims, of screening agents that may affect a phenotype of said mouse as provided by the instant

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specification and encompassed by the claims, does not appear to be specific and substantial. The asserted utility does not appear specific and substantial to the skilled artisan since the evidence of record has not provided any suggestion of a correlation between any RPTPB, embryonic lethality, and any disease or disorder. Since the evidence of record has not provided a correlation between embryonic lethality and any disease or disorder, the utility of identifying agents that affect embryonic lethality is not apparent. The evidence of record has not provided any other utilities for the transgenic mouse embraced by the claims that are specific, substantial, and credible.

The asserted utility of the transgenic mouse embraced by the claims is based on the expectation that disrupting the nucleotide sequence set forth in SEQ ID NO: 1 would result in a detectable phenotype in the mouse. The phenotype observed in the transgenic mice embraced by the claims is embryonic lethality. While the phenotypes exhibited by the claimed transgenic mouse are contemplated to be associated with a disease, the association of embryonic lethality with any disease has yet to be elucidated. In fact the art suggests that phenotypes, such as embryonic lethality, are greatly influenced by the genetic background of the transgenic knockout mouse. For example, Casademunt et al report (EMBO, 1999, 18(21): 6050-6061) *nrf1*^{-/-} mice exhibit differences in embryonic lethality that appear dependent on the genetic background of the mouse. In short, transgenic *nrf1*^{-/-} mice in a BL6 background cannot survive past E12 while in an Sv129 background such transgenic mice are viable and healthy to adulthood. See the abstract and throughout the entire document. Furthermore, LeCouter et al (Development, 1998, 125: 4669-4679) observe that a null

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mutation in a p130 is lethal at E11-13 on a Balb/cJ background but when such a mutation is crossed onto a C57BL/6 background the resulting mice are viable and fertile. See the abstract and throughout the entire document. More to the point, Harroch et al (Molecular and Cellular Biology, 2000, 20(20): 7706-7715; IDS) discuss that an RPTPB null mutation crossed into a Swiss Webster genetic background result in mice having no obvious abnormalities. See the abstract and throughout the entire document. The instant specification has taught use of ES cells from a 129/OlaHSD genetic background to generate chimeric mice, which were then bred onto a C57BL6 genetic background to produce the instantly claimed mice exhibiting embryonic lethality as homozygous embryos. See pages 50-51 of the instant specification.

Therefore, the references suggest a need to provide independent evidence of an association of embryonic lethality with a disease or disorder. However, neither the specification nor any art of record provides evidence of the existence of a correlation between embryonic lethality and a disease or disorder, leaving the skilled artisan to speculate and investigate the uses of the transgenic mouse embraced by the claims. The specification essentially gives an invitation to experiment wherein the artisan is invited to elaborate a functional use for the transgenic mouse embraced by the claims. In light of the above, the skilled artisan would not find the asserted utility of the transgenic mouse embraced by the claims to be specific and substantial.

Claim Rejections - 35 USC § 112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 14, 25-38, and 40-41 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a substantial and specific asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

In addition the following additional rejections are necessitated under 35 U.S.C. 112, first paragraph:

Both the specification and the state of the art have taught that the transgenic knockout technology requires the use of embryonic stem cells that have been genetically manipulated to comprise a disruption in a nucleotide sequence of interest. The specification has not taught creation of a transgenic knockout mouse by methods that do not require embryonic stem cells. Presently, the transgenic knockout technology is limited to the mouse system. See below.

With regard to the claim breadth, claims 38 and 40 embrace murine embryonic stem cells, which encompass species other than mice, such as rats and gerbils. The specification fails to teach use of embryonic stems from species other than mice. It is well known in the knockout art that the production of knockout animals other than mice is undeveloped. This is because ES cell technology is generally limited to the mouse

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system, at present, and that only "putative" ES cells exist for other species. See Moreadith et al. at page 214, Summary. Seamark (Reproductive Fertility and Development, 1994) supports this observation by reporting that totipotency for ES cell technology in many livestock species has not been demonstrated (page 6, Abstract). Likewise, Mullins et al (Journal of Clinical Investigation, 1996) state, "although to date chimeric animals have been generated from several species including the pig, in no species other than the mouse has germline transmission of an ES cell been successfully demonstrated." (page S38, column 1, first paragraph). Furthermore, claims 25-38 as written do not appear to require germline transmission of the disrupted nucleotide sequence. These claims may be broadly interpreted to read on a single cell comprising a disrupted nucleotide sequence. Since the claims do not require germline transmission of the disrupted nucleotide sequence it would be unpredictable if an ES cell comprises the disrupted nucleotide sequence. The evidence of record does not support germline transmission of non-ES cells. Also, it would be unpredictable if a disruption of a nucleotide sequence in a single cell would result in a phenotype; the instant specification has not provided any uses for a transgenic mouse that does not exhibit a phenotype resulting from disruption of a nucleotide sequence (see below). Amending the claims to read on a "transgenic mouse whose genome comprises" would be sufficient to suggest germline transmission. Given the unpredictable state of the art it would have required undue experimentation for the skilled artisan to create transgenic knockout non-human animals of species other than the mouse.

Claims 14 and 25-27 encompasses transgenic mice that comprise a disruption in a RPTPB gene, particularly the nucleotide sequence set forth in SEQ ID NO: 1, that do not exhibit any particular phenotype. Claims 14 and 28-38 embrace transgenic mice exhibiting a particular phenotype, wherein a broad interpretation of the claimed animals could read on disruption of a RPTPB gene in a single cell. Claims 14, 25 and 27-38 embrace transgenic mice comprising a heterozygous disruption of an RPTPB gene. The specification has taught that transgenic mouse embryos whose genomes comprise a homozygous disruption of the RPTPB gene exhibit a phenotype of embryonic lethality. The specification has not provided guidance correlating to a phenotype in the other transgenic mice embraced by the claims. The state of the art at the time of filing was such that one of skill could not predict the phenotype of a knockout mouse (Moreadith et al., 1997, J. Mol. Med., Vol. 75, pages 208-216; see page 208, column 2, last full paragraph). Also see Leonard et al (Immunological Reviews, 1995, pages 97-114) who discuss that inactivation of the gene encoding cytokine receptor γ chain in transgenic mice results in a phenotype different from that expected. Finally, Moens et al. (Development, Vol. 119, pages 485-499, 1993) disclose that two mutations produced by homologous recombination in two different locations of the N-myc gene produce two different phenotypes in mouse embryonic stem cells, one leaky and one null (see abstract). The specification has asserted that the nucleotide sequence set forth in SEQ ID NO: 1 encodes a RPTPB. However, it would be difficult to predict any phenotype resulting from disruption of the sequence of SEQ ID NO: 1 in light of the above. Moreover, as the claims read on disruption of a RPTPB gene in a single cell, it would be

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unpredictable if such a disruption would result in any phenotype. The specification discloses a phenotype exhibited by transgenic mouse embryos whose genome comprises a homozygous disruption in the nucleotide sequence set forth in SEQ ID NO: 1 is embryonic lethality. See pages 50-52 of the specification. Claims 14 and 25-27 as written, do not include a phenotype that differs from the wild-type mouse. One of skill in the art would not know how to use a transgenic knockout non-human animal that lacks a phenotype, particularly because the instant specification has not provided uses for such; the transgenic mice that have a phenotype may be used for drug testing according to the instant specification. The claims (14, 25 and 27-38) embracing heterozygous mice are not enabled as the specification has not disclosed a phenotype for such and because as previously stated, the skilled artisan would not know how to use a transgenic mouse lacking a phenotype. Accordingly, the claims are not commensurate in scope with the phenotype disclosed in the specification. Given the unpredictable nature of a phenotype that results from disruption of a nucleotide sequence it would have required undue experimentation for the skilled artisan to make and use the invention as claimed.

It is noted that the claims, which embrace a homozygous disruption of the RPTPB gene, are directed to a transgenic mouse. However, use of transgenic mouse language implies a full term mouse was created. This language appears inconsistent with the teachings of the specification because it appears that the homozygous mouse embryos did not mature to term given the phenotype of embryonic lethality.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 14 and 25-27 are rejected under 35 U.S.C. 102(a) as being anticipated by Harroch (IDS).

The claims are directed to a transgenic mouse comprising a disruption in an RPTPB gene.

Harroch et al teach transgenic mice comprising a homozygous disruption in the RPTPB gene.

Accordingly, Harroch et al anticipate all of the instant claim limitations.

Conclusion

No claim is allowed.

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Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Peter Paras, Jr., whose telephone number is (571) 272-0732. The examiner can normally be reached Monday-Friday from 8:30 to 4:30 (Eastern time).

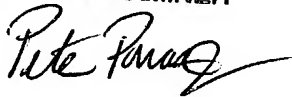
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson, can be reached at 571-272-0804. Papers related to this application may be submitted by facsimile transmission. Papers should be faxed via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Official Fax Center number is (703) 872-9306.

Inquiries of a general nature or relating to the status of the application should be directed to Dianiece Jacobs whose telephone number is (571) 272-0532.

Peter Paras, Jr.

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**PETER PARAS, JR.
PRIMARY EXAMINER**

A handwritten signature in black ink, appearing to read "Pete Paras", with a stylized flourish extending from the end.